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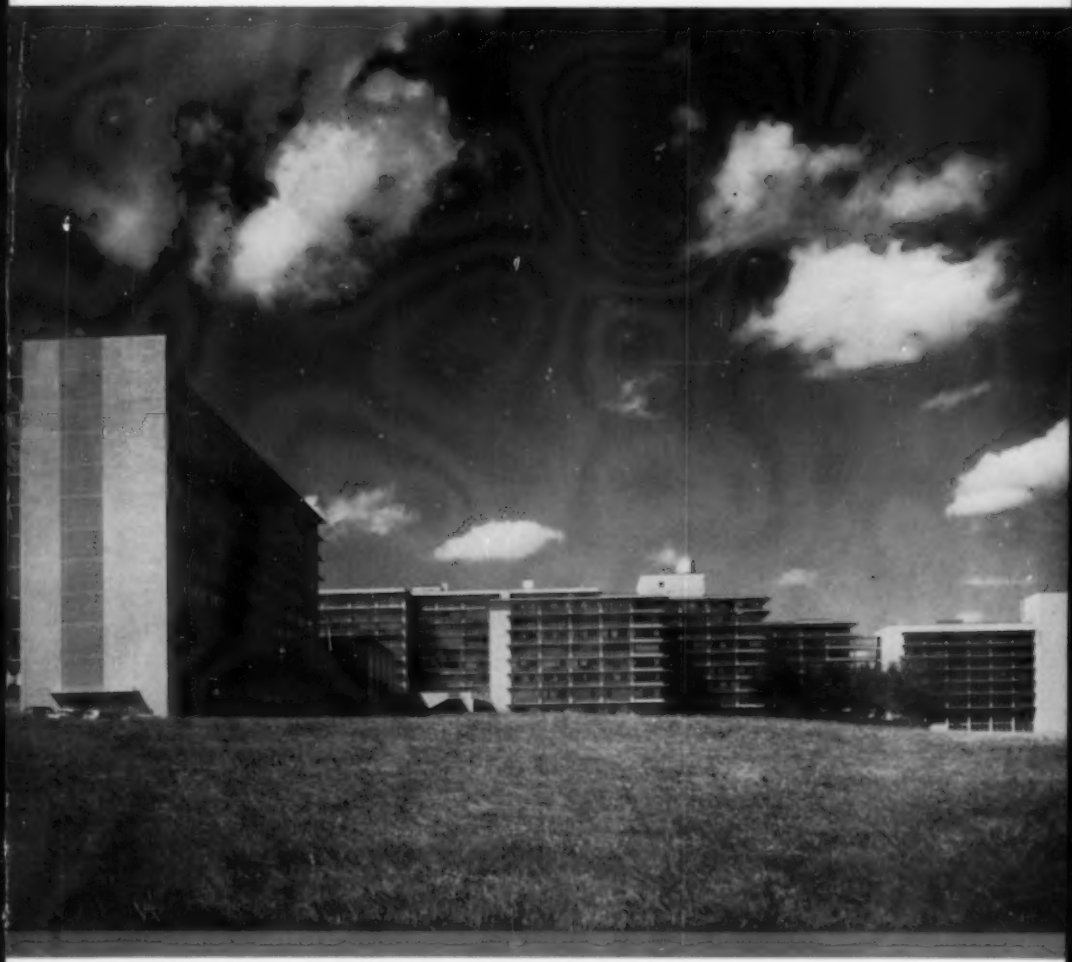

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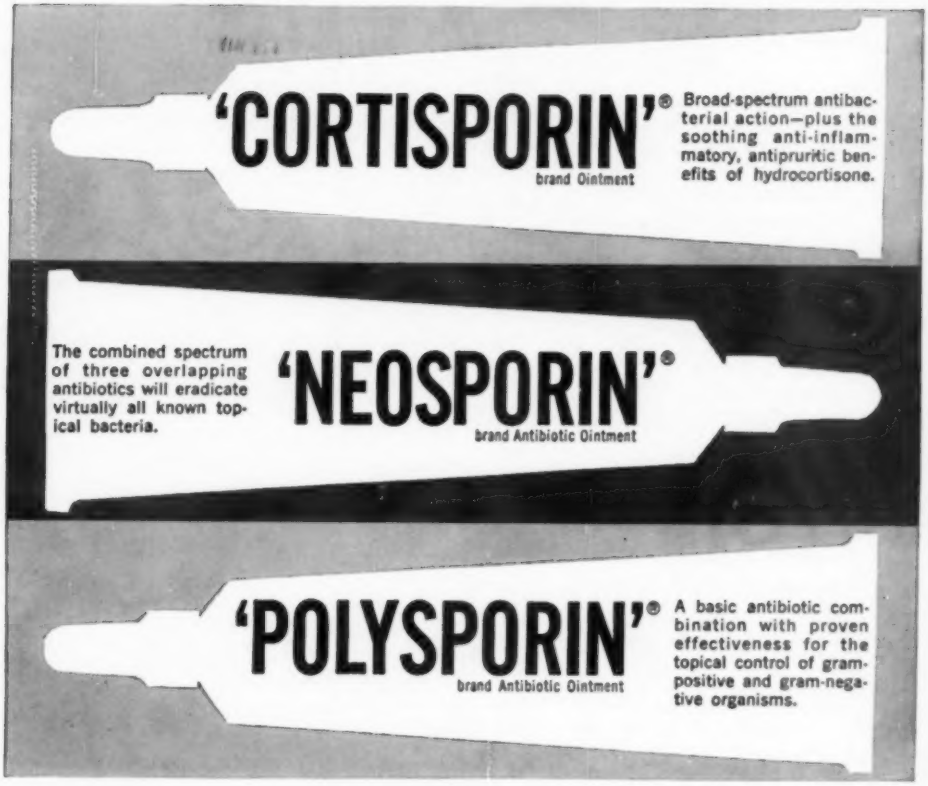
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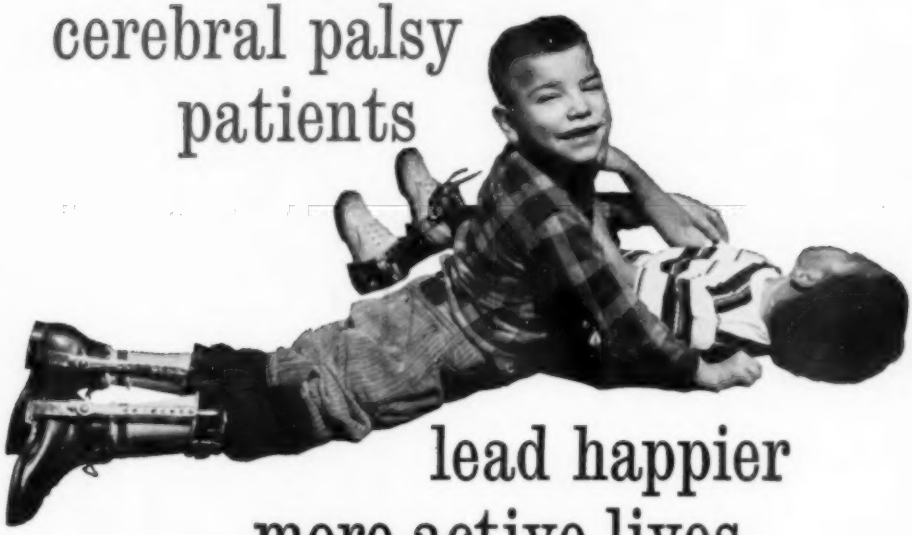

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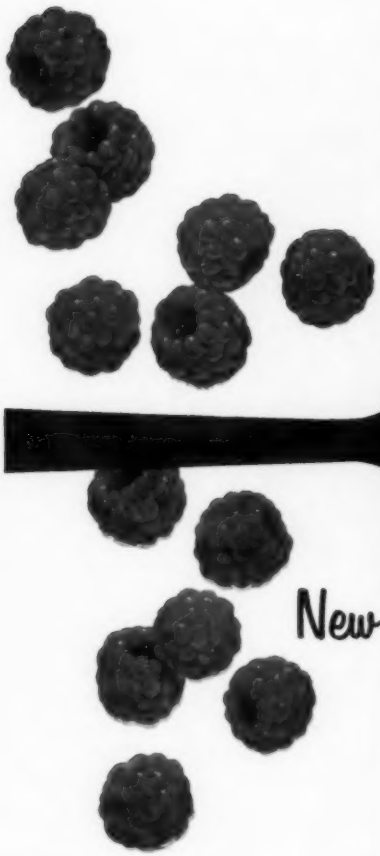

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Current Views on the Diagnosis and Treatment of the More Common Forms of Bacterial Meningitis*

EMANUEL APPELBAUM, M.D.**
New York

IT is well known that the advent of sulfonamides and antibiotics has completely revolutionized the treatment of bacterial meningitis. However, in recent years physicians have become confused because of the introduction of many new chemical and antibiotic agents. Furthermore, since chemotherapy is specific in nature, accuracy in diagnosis becomes a matter of prime importance. The purpose of this paper is to discuss briefly the salient diagnostic features and the newer developments in the therapy of the more common forms of bacterial meningitis.

CLINICAL MANIFESTATIONS

The symptoms and signs of the various forms of bacterial meningitis are very much the same, with certain exceptions that will be noted presently. In the pyogenic forms, the disease generally is ushered in suddenly with intense headache, vomiting and fever, and often with chills. The onset is more apt to be insidious in tuberculous meningitis. On rare occasion a patient may be practically afebrile. Convulsions may occur especially in young children. A polymorphous or hemorrhagic skin eruption is frequently found in meningococcic meningitis, especially during epidemic outbreaks. Hemorrhagic skin lesions are also encountered on occasion in meningitis due to *H. influenzae*. The mental condition is subject to the widest variations. In rather mild cases the mentality may be practically normal, except for some irritability and restlessness. In more severe cases there may be delirium, lethargy, semistupor, or even coma, early in the disease. Hypertonicity of muscles is manifested by the presence of varying grades of neck rigidity and positive Brudzinski and Kernig signs. Paralysis of the muscles of the eyes or of the face occasionally occurs. Extremity paralysis or

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** Professor of Clinical Medicine, New York University Postgraduate Medical School; Visiting Physician, Bellevue and University Hospitals; Chief, Division of Acute Infections of the Central Nervous System, New York City Health Department

hemiparesis may be encountered in tuberculous meningitis or when the meningeal infection is associated with brain abscess. Bulging of the fontanel is an early and important sign in infants. Early in the course of meningitis the tendon reflexes are apt to be exaggerated and equal. Later they may become unequal, diminished and finally lost. Ophthalmoscopic examination often shows moderate congestion and on rare occasion, choking of the discs. In tuberculous meningitis, choroidal tubercles may be found in the fundi.

It is important to note that in infants one does not see early stiffness of the neck, the presence of Brudzinski or Kernig signs, or conspicuous changes in the reflexes. There is often vomiting and practically always some intestinal disturbance. Some time often elapses before symptoms develop that direct the physician's attention to the central nervous system. These may be the development of strabismus, a fairly well-defined rigidity of the neck, or severe convulsions. At times a bulging fontanel will lead the physician to suspect the presence of meningeal disease.

Of special interest is the clinical picture in the fulminating form of meningococcus infection, known as the Waterhouse-Friderichsen syndrome. This condition is characterized by the presence of an overwhelming bacteremia together with profound circulatory collapse. The cardinal clinical features are fever, widespread hemorrhagic skin lesions which coalesce into large ecchymotic areas, marked cyanosis, hyperpnea, signs of peripheral vascular collapse, and rapid death of the patient. These patients often show only a minimal degree of meningeal involvement.

LABORATORY STUDIES

The analysis of the spinal fluid is the most important laboratory procedure in making a diagnosis of meningitis. In pyogenic meningitis the cells are usually greatly increased with a large preponderance of polymorphonuclears. On rare occasion the fluid contains few or no cells. In tuberculous meningitis there is usually a moderate increase in cells, predominantly mononuclears. It is important to stress that the differential cell count should be done on a stained smear and not on the counting chamber.

The spinal fluid protein is increased from a moderate to a marked degree in different cases. Forty mg. of protein per 100 cc. of spinal fluid is generally regarded as the upper limit of normal. The sugar in the spinal fluid may be normal at the onset of the meningitis. As

the disease progresses the amount of sugar usually decreases markedly or disappears entirely. With subsidence of the meningeal infection, the sugar returns to normal. The normal range of sugar in the spinal fluid is from 40 to 80 mg. per 100 cc. It should be emphasized that a determination of the blood sugar is essential to the correct interpretation of the spinal fluid sugar values, especially in borderline cases.

The bacteriologic study is by far the most important part of the spinal fluid examination. In many cases varying numbers of organisms will be found in the stained smear. It has been my experience however, that the stained smear alone is unreliable in the diagnosis of purulent meningitis, since the organisms are often pleomorphic and irregular in staining properties. Therefore it is necessary to base the diagnosis on the results of the culture or on the identification of the organisms directly from the spinal fluid by the quellung reaction. In the last named test a swelling of the organism's capsule is produced by specific antiserum. In tuberculous meningitis the diagnosis may be confirmed bacteriologically by finding acid-fast bacilli in the stained smear or by recovering *Mycobacterium tuberculosis* from the spinal fluid culture.

There are other useful laboratory procedures. A blood culture should always be performed on every patient with pyogenic meningitis, since the etiologic agent can sometimes be recovered from the blood when the spinal fluid culture is sterile. In occasional cases of meningococcic meningitis, the organisms may be isolated from hemorrhagic skin lesions, the nasopharynx, the conjunctivae or joint exudate.

In 1944 Falk and Appelbaum[1] described a simple method for demonstrating agglutinins in the serums of individuals suffering from meningococcic infection. In subsequent studies these authors[2,3] found agglutinins in significant titers for one or more of the types of meningococci in a high percentage of bacteriologically proved cases of meningococcic infection and in clinically typical cases lacking such proof. Agglutinins were observed more regularly during the subacute than during the acute phase and reached their maximum titers early in the convalescent phase. As recovery progressed there was a general decrease in the agglutinin titer. It thus became apparent that for optimum results successive specimens must be tested during the various phases of the disease. When such serial tests were made on three or more specimens, the mag-

nitude of positive results exceeded 95 per cent. These studies indicated the usefulness of the meningococcus agglutination test as a diagnostic procedure in cases of clinically typical meningococcic infection which lacked bacteriologic proof. The importance of performing serial tests to demonstrate the changes in the agglutinin titer cannot be overemphasized.

TREATMENT

MENINGOCOCCIC MENINGITIS

Prior to the introduction of serum the mortality rate in this disease varied from 20 to 90 per cent.[4] The general use of antiserum improved the situation only moderately. The introduction of sulfonamides however, has altered markedly the status of this disease and has resulted in a striking reduction in mortality.

Choice of Drug.—All the sulfonamides are effective therapeutically against the meningococcus. Thus far, strains of meningococci resistant to sulfonamides have not been encountered.[5] Because of its high rate of absorption, excellent diffusion through the meningovascular barrier, and reduced toxicity, sulfadiazine generally has been regarded as the most suitable sulfonamide in the treatment of purulent meningitis. In order to minimize the danger of renal drug reactions, some workers[6,8] have favored the use of sulfonamide mixtures or the highly soluble sulfonamides as sulfisoxazole (Gantrisin), sulfisomidine (Elkosin) and sulfamethylthiadiazole (Thiosulfil). While toxic manifestations are apparently less frequent with sulfonamide mixtures and the more soluble sulfonamides, sulfadiazine has the advantage of yielding higher spinal fluid levels. The long-acting sulfonamides, such as sulfamethoxypyridazine (Kynex) and sulfadimethoxine (Madribon) have not had sufficient clinical trial for proper evaluation.

Dosage and Administration.—The discussion on the method of using sulfonamides is based on my experience with sulfadiazine. After trying out widely varied schemes of dosage, I have adopted the following plan:

On the first day of treatment children under one year of age receive from 2 to 3 Gm.; children from one to three years of age receive from 3 to 4 Gm.; children above that age receive from 4 to 7 Gm., and adults receive from 8 to 10 Gm. One quarter to one third of this amount is given as the initial dose, and the remainder is divided and administered at intervals of four hours.

The drug may be given orally, intravenously or subcutaneously. For parenteral medication, the sodium compound is used in a 5 per cent solution in distilled water or in 1/6 molar sodium lactate. It is my belief that the parenteral routes should be reserved for the severe cases and for those patients who are unable to take or retain oral medication. There is no indication for the use of the drug intrathecally. In my opinion it is dangerous to make the first dose a massive one, especially when given by vein. Similarly, it is undesirable to give large amounts of the drug simultaneously by vein and by mouth. After the first twelve to twenty-four hours, the patient is, as a rule, able to take the medication orally, and he continues to receive the drug at four-hour intervals. In the use of the drug after the first day, one is guided by the clinical condition of the patient and the concentration of sulfonamide in the blood.

It is essential that during the course of sulfonamide therapy the patient should receive a sufficient amount of fluid and an adequate amount of alkalis, particularly when large doses of the drug are administered intravenously. I recommend the administration of at least 3,000 cc. of fluids a day in order to insure a urinary output of 1,200 cc. or more daily. The addition of alkalis is not necessary when one employs the highly soluble sulfonamides.

Results.—Generally, the patients show striking clinical improvement on the second or third day of chemotherapy. In most instances the fever drops by crisis within twenty-four to forty-eight hours. An even more precipitous drop in temperature to normal within four to six hours is occasionally observed. In some cases the fall in temperature is by a rapid lysis extending over a period of three to six days. While subjective improvement is apparent early, the abnormal neurologic signs usually persist for a longer period. Indeed, nuchal rigidity not infrequently lasts well into convalescence. In my experience, the recovery rate in meningococcic meningitis has been 96 per cent following the use of sulfonamides.

Treatment of the Fulminating Form of the Disease (Waterhouse-Friderichsen Syndrome).—For many years this grave form of the disease was considered uniformly fatal. However, with the advent of sulfonamides it has been possible to achieve recovery in some of these cases by prompt institution of the chemotherapy in combination with drugs that counteract the peripheral vascular collapse. The latter agents have included adrenal cortical extract, cortisone, hydrocortisone, corticotropin, prednisone, and l-norepinephrine.

Contrary to the general impression, the effects of the adrenal cortical extract, when used in relatively large amounts, compare favorably with those of cortisone and hydrocortisone. In a group of 28 fulminating cases treated with chemotherapy and adrenal cortical extract, I obtained 18 recoveries. Of eight subsequent patients treated with cortisone, alone or in combination with other steriods, with or without norepinephrine, five recovered and three died. While several investigators[9,11] recently have cast doubt on the value of the adrenal substitution therapy and have stressed the importance of l-norepinephrine, my results strongly favor the use of adrenal hormones. At present I recommend the following plan of treatment:

On admission the patient receives an intravenous infusion of 1,000 to 1,500 cc. saline and 5 per cent dextrose together with 100 to 200 mg. of hydrocortisone. At the same time l-norepinephrine, 4 mg. per liter of diluent, is administered intravenously with the rate of flow adjusted to maintain the blood pressure above the shock level. The antibacterial therapy consists of the prompt administration by vein of sodium sulfadiazine or sulfisoxazole in accordance with the schedule described above and the injection of aqueous penicillin intramuscularly, 500,000 to 1,000,000 units every two hours. The saline infusion, together with the hydrocortisone, is repeated in twelve hours. Instead of hydrocortisone one may use 200 to 300 mg. of cortisone or 50 to 100 cc. of adrenal cortical extract per day. Subsequent treatment includes continuation of the combined chemotherapy and the use of 25 to 50 mg. of cortisone intramuscularly or orally every six hours. Prednisone may be substituted for cortisone for oral medication. Usually the steroids can be discontinued after three or four days. Whole blood transfusions and other supportive measures may be used as indicated by the needs of the individual patient.

Toxic Effects of Sulfonamide Therapy.—It is still necessary to direct attention to the toxic potentialities of the sulfonamide drugs. The most common toxic reactions are related to the urinary tract and consist of hematuria and oliguria or anuria. As a rule, these reactions clear up rapidly after withdrawal of the sulfonamides. Closer attention to adequate fluid intake and the concomitant use of a sufficient amount of alkali have contributed greatly to the reduced incidence of renal reactions. Other side-effects include drug fever, hematologic reactions, skin eruptions and drug encephalopathy. The appearance of any of these reactions is an indication for the immediate cessation of the chemotherapy.

In this connection I wish to comment on the syndrome of encephalopathy resulting from sulfonamide intoxication. This complication is usually difficult to recognize and to differentiate from the symptomatology of the meningitis. The onset of this condition is early in the course of treatment, usually on the second or third day. The clinical picture is characterized mainly by varying grades of stupor, often progressing to deep coma. Occasionally there are delirium, hallucinations or convulsions. These symptoms are invariably accompanied by a significant rise in temperature. Examination of the spinal fluid during the development of the intoxication will show definite evidence of improvement in the meningitis. Withdrawal of the drug will result in a drop in temperature and clearing of the mental state.

Remarks on Antibiotic Therapy.—I have used penicillin, the various tetracyclines, chloramphenicol and erythromycin, either singly or in combinations or combined with sulfonamides in the treatment of 177 cases of meningococcic meningitis and have obtained 170 recoveries and 7 deaths. The disease obviously responds to antibiotics but in a less dramatic manner than it does to sulfonamide therapy. I have already referred to the possible value of penicillin as an adjuvant to sulfonamides in the therapy of the fulminating form of the disease. The antibiotics are particularly valuable in the treatment of patients who are hypersensitive to sulfonamides or have developed a sulfonamide intoxication.

PNEUMOCOCCIC MENINGITIS

Before the sulfonamides became available the fatality rate in pneumococcic meningitis was 100 per cent in my experience. With the advent of these drugs, particularly sulfapyridine and sulfadiazine, the prognosis for patients with meningitis of this type was considerably improved. In a series of 60 cases of pneumococcic meningitis treated with sulfonamides, Hodes and his associates[12] reported a recovery rate of 42 per cent. An even greater advance was marked by the introduction of penicillin, which has since been considered the drug of choice in the treatment of pneumococcic meningitis. However, there has been considerable difference of opinion among investigators regarding the need of administering the antibiotic intrathecally as well as systemically. Much light has been shed on this problem by Dowling and his associates[13] who have shown that in treating pneumococcic meningitis with massive doses of penicillin administered systemically, adequate levels of the

drug are obtained in the cerebrospinal fluid, thereby obviating the need for intrathecal medication. These authors have recommended the administration of one million units of penicillin intramuscularly at two-hour intervals. Most investigators generally have followed this plan of treatment. In my earlier studies[14,15] I favored the use of penicillin intramuscularly and intrathecally, but I have since abandoned the intrathecal medication.

There is at present no unity of opinion with respect to the adjunctive use of sulfonamides. I agree with Dowling and his collaborators[13] who believe that sulfonamides are not necessary when large doses of penicillin are used. However, most clinicians still prefer to employ sulfonamides as adjuvants.

There is also much uncertainty regarding the value of antibiotics other than penicillin in the treatment of pneumococcic meningitis. Several reports have appeared on the successful treatment of this form of meningitis with the tetracyclines, chloramphenicol, and erythromycin.[16,19] I have not used any of these drugs alone, but I have used them in combination with penicillin in the treatment of a small number of patients with pneumococcic meningitis. The results of the combined therapy were not superior to those obtained with penicillin alone.

At present it is my belief that pneumococcic meningitis might best be treated with large doses of aqueous penicillin without the use of adjuvant drugs. I recommend the intramuscular administration of one million units of the antibiotic every two hours. In infants and young children, one half of this dose is generally sufficient. The total daily dose of the antibiotic may also be given intravenously, using a continuous saline infusion drip method. The administration of the drug is, as a rule, continued for a period of five to seven days after clinical improvement is manifest and the spinal fluid no longer shows organisms or diminution in the sugar content. The recovery rate with this regimen has been 78 per cent.

In a recent paper Ribble and Braude[20] reported favorable results from the use of ACTH and steriods in conjunction with penicillin in the treatment of twelve cases of pneumococcic meningitis. Evaluation of the role of the hormones in these cases is very difficult, since the authors employed massive doses of penicillin. Furthermore, their series is too small for definite conclusions.

The intrathecal use of streptokinase and streptodornase and more recently pancreatic desoxyribonuclease in pneumococcic and other

forms of bacterial meningitis has been reported by several investigators.[21,24] In my opinion this subject requires further study, and in the present state of knowledge the use of any of these enzymes is not recommended.

H. INFLUENZAE MENINGITIS

Prior to the advent of chemotherapy the mortality in influenzal meningitis varied from 90 to 100 per cent. The status of the disease has been altered considerably by the use of sulfonamides and specific rabbit antiserum. The introduction of streptomycin and the broad spectrum antibiotics marked further advances. Indeed, by means of antibiotic therapy it is now possible to cure almost all cases of H. influenzae meningitis. Since the influenza bacillus is highly susceptible to the action of several antibiotics, the physician has at his disposal a number of very effective agents for the treatment of meningitis due to this organism. There is however, no unity of opinion regarding the drug of choice. Pediatricians generally have favored the use of chloramphenicol. However, streptomycin and the tetracyclines are also very effective.

There can be no doubt that the antibiotics under consideration are all efficacious in the therapy of H. influenzae meningitis and yield a recovery rate of 96 per cent. At present I am inclined to regard streptomycin and chloramphenicol as the more effective agents. In my opinion, the main advantage of chloramphenicol is that it can be given orally. When streptomycin is used, it is not necessary to administer it intrathecally. There is apparently no additional benefit from the employment of combinations of antibiotics or from the adjunctive use of sulfonamides.

The recommended dosage schedule for the various antibiotics is as follows:

Streptomycin is given intramuscularly, using a dose of ½ to 1 Gm. per day, depending on age.

Chloramphenicol can be used intravenously, intramuscularly or orally. It is often a good plan to administer the first three or four doses parenterally and then orally. The average daily dose of the drug is 100 mg. per Kg. of body weight. At times it is necessary to raise the dosage to 150 and even 200 mg. per Kg. Parenteral treatment generally is given at eight or twelve-hour intervals and oral medication at six-hour intervals.

Tetracyclines may be used parenterally or orally. It is advisable

to initiate with parenteral and follow with oral medication. The daily tetracycline dosage is 50 to 60 mg. per Kg. administered at six or eight-hour intervals.

With all regimens, treatment is continued for a period of five to seven days after the temperature has become normal and the spinal fluid no longer shows organisms or diminution in the sugar content.

STREPTOCOCCIC MENINGITIS

Before the advent of chemotherapy the case fatality rate in streptococcic meningitis was more than 95 per cent. The use of sulfonamides has reduced this mortality rate to about 35 per cent. With the introduction of penicillin the prognosis for patients with meningitis of this type was further improved. At present penicillin is regarded as the drug of choice in the therapy of streptococcic meningitis. The antibiotic should be employed in accordance with the schedule recommended for pneumococcic meningitis. In cases of meningitis due to enterococcus, it is advisable to combine the penicillin with 2 Gm. of streptomycin daily. The treatment for streptococcic meningitis should be continued for five to seven days after the spinal fluid has become sterile and all clinical evidence indicates that the infection has subsided.

STAPHYLOCOCCIC MENINGITIS

Occasional recoveries in staphylococcic meningitis have followed the use of sulfonamides. In most instances however, the patients have not responded to sulfonamide therapy. Penicillin has yielded more satisfactory results and for a number of years has appeared to be the drug of choice in the treatment of this form of meningitis. However, the sensitivity of staphylococci to penicillin has decreased steadily. For a while penicillin-resistant staphylococci were susceptible to several new antibiotics as they became available. These included streptomycin, chloramphenicol, the various tetracyclines, erythromycin, bacitracin, novobiocin and ristocetin. However, ample evidence is accumulating to indicate that with continued usage the newer antibiotics are steadily becoming less effective in staphylococcic diseases.[25,29]

The choice of antibiotic treatment in staphylococcic meningitis therefore depends on the results of sensitivity tests. If the staphylococcal strain is highly sensitive to penicillin, this antibiotic should be used in accordance with the schedule recommended for pneumo-

coccic meningitis, namely 12 million units of the drug daily, administered parenterally. In infections caused by an organism with moderate or slight penicillin sensitivity, much larger doses of the antibiotic are required, generally 20 to 40 million units per day, administered by continuous intravenous drip. When the causative staphylococcus is penicillin-resistant, it seems best to use large doses of penicillin in combination with other antibiotics to which the organism shows sensitivity. The latter generally include erythromycin 2 to 4 Gm., chloramphenicol 2 to 3 Gm., novobiocin 2 Gm. and bacitracin 50,000 to 100,000 units per day. Of the newer antibiotics the more promising appear to be ristocetin and vancomycin, each of which is administered intravenously, 2 to 3 Gm. per day. The use of the new synthetic penicillin, Staphcillin, is not recommended because of its poor passage across the blood-brain barrier. With all regimens treatment is continued for at least two weeks, even though clinical improvement and return of the spinal fluid findings to normal may have become apparent earlier.

TUBERCULOUS MENINGITIS

Prior to the advent of chemotherapy, tuberculous meningitis was almost invariably fatal. The status of the disease has been altered considerably by the use of streptomycin, administered intramuscularly and intraspinally. By means of this antibiotic regimen, combined frequently with other tuberculostatic agents, remarkable results have been achieved that yielded a high rate of remissions. After prolonged observation however, the end-results were discouraging, since there were few long-term survivors. The introduction of isonicotinic acid hydrazides has marked a great advance in the therapy of tuberculous infections, particularly of the miliary and meningeal forms.

At present the regimen most commonly employed in the therapy of tuberculous meningitis is a combination of isoniazid, streptomycin and para-aminosalicylic acid. The daily dose of isoniazid is generally 10 to 20 mg. per Kg. of body weight, of streptomycin 1 Gm. and of para-aminosalicylic acid 6 to 12 Gm. I have also treated a number of patients with hydrazides alone.

The accompanying table shows the results obtained in 80 patients with tuberculous meningitis who were treated with isonicotinic acid hydrazides, alone or in combination with streptomycin and para-aminosalicylic acid. Although it is difficult to compare two groups

that are numerically disproportionate, nonetheless it may be noted that the patients who were treated with hydrazides alone fared as well as did the patients on the combined therapy. Of special interest is the fact that no meningeal relapse occurred in any of the patients while receiving hydrazides. It is apparent that the hydrazides are the main agents in the therapy of tuberculous meningitis.

In recent years several workers[30,37] have reported on the use of combined hormone-antimicrobial therapy in tuberculous meningitis. Most of these investigators believe that the hormones are beneficial and none has found them to be harmful. It was difficult to appraise the value of the adjuvant steroid therapy employed in 15 of the 80 cases recorded in the table. The subject of hormonal therapy in this disease undoubtedly requires further study.

Results Obtained in 80 Cases of Tuberculous Meningitis Treated with Hydrazides, Alone or in Combination with Streptomycin and Para-aminosalicylic Acid

Regimen	No. of Cases Treated	No. Recovered	No. Died	Recovery %
Hydrazides alone	20	15	5	75
Hydrazides combined with streptomycin and para-aminosalicylic acid	60	41	19	68
Total	80	56	24	70

SUMMARY

I have discussed the diagnostic aspects and the newer methods of treatment of the more common forms of bacterial meningitis. The major symptomatology includes headache, vomiting, fever, convulsions, change in the mental state, and signs of meningeal irritation. In meningococcic infection there is frequently a polymorphous or hemorrhagic skin eruption. The diagnosis of meningitis is often delayed in infants who display less characteristic signs of meningeal irritation.

In all forms of meningitis an accurate diagnosis of the etiologic agent requires immediate bacteriologic studies on the spinal fluid. The meningococcus agglutination test is a useful diagnostic procedure in cases of clinically typical meningococcic infection which lack bacteriologic proof.

The development of chemotherapy and the introduction of the various antibiotics are responsible for the highly successful results obtained in the treatment of the more common forms of bacterial meningitis. The sulfonamides are the best chemotherapeutic agents for meningococcic infection. The drug of choice in the treatment of pneumococcic and streptococcic meningitis is penicillin, administered systemically only. For the treatment of meningitis due to H. influenzae several very effective agents are available, including streptomycin, chloramphenicol, and the tetracyclines. The treatment of staphylococcic meningitis is a difficult problem because of the high incidence of penicillin-resistant staphylococci. Antibiotic therapy in this form of meningitis depends mainly on the results of sensitivity tests. The regimen most commonly employed in the therapy of tuberculous meningitis is a combination of isoniazid, streptomycin and para-aminosalicylic acid.

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Carphenazine in Mental Defectives
A Specific Antiemetic

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The ever-growing number of effective phrenotropic agents should make it increasingly possible to direct therapy to solution of a particular problem. In previous reports,[1-10] we have evaluated several agents which seemed to hold promise in alleviating some of the symptoms associated with brain damage. Their subsequent use in our mentally defective juvenile population has reduced hyperactivity, agitation and aggressiveness, improved behavior in the wards and cottages, lessened the number and severity of epileptic seizures, and produced a good degree of muscular relaxation in spastics.

Since brain-damaged patients remain permanently hospitalized even when such secondary difficulties are ameliorated, they provide an ideal clinical environment for the comparison of therapeutic agents. At Sunland Training School our program since 1956 has been designed with a two-fold objective: to search out those psychopharmacologic compounds that can be used to attack specific problems; and on the other hand, to develop a standard chemotherapeutic regimen for use in our institution.

Recent investigations with the phenothiazine derivatives of the piperazinyl series have shown them to be potent tranquilizers with low sedative but high antiemetic activity.[11-13] The newest is carphenazine†, which has been reported in animal studies to cause few extrapyramidal by-effects or toxic side reactions.[14] It has peripheral antiadrenergic and anticholinergic properties, a central antiadrenergic action, with a marked ability to reduce motor activity. Although the principal application of this compound to date has been in chronic, hypodynamic schizophrenics,[15] the described properties interested us in trying it in our patients.

*From Sunland Training Center at Gainesville, Fla.
†Carphenazine is available as Proketazine®, from Wyeth Laboratories.

SCOPE AND METHOD

Most of our 600 patients have extensive brain damage, mainly through birth injury, infection, congenital anomalies or faulty cranial development. Their physical handicaps are combined with various degrees of mental retardation and emotional difficulty. Severe autonomic nervous system disturbances are frequent. Approximately 75 per cent are spastic children and adolescents and 60 per cent have seizures. About 45 per cent have some developmental anomaly or a history of birth injury. Many exhibit problem behavior, such as overactivity, combativeness, destructiveness, frequent temper tantrums, persistent crying or masturbation.

Two of our greatest problems with brain-damaged patients have been spasticity and vomiting. The vomiting has been intractable to every measure, including all antiemetics and even surgery. The reverse peristalsis which occurs is evidently related to the brain damage, possibly due to direct stimulation of the vomiting center in the medulla from increased intracranial pressure. Some patients vomit from esophageal swallowing, or choke on food because of difficulty in using the muscles involved. The periodicity varies; for example, some can retain food two or three days but then vomit persistently for the next three or four.

A total of 110 brain-damaged patients were selected for study. The majority were spastic, with about equal numbers of the tonic and athetoid types, and many were also epileptic or mentally deficient. The group included a few hydrocephalics, mongoloids, phenylketonurics, porencephalics, and some whose brain damage was due to congenital syphilis, German measles in the mother, or to infections such as encephalitis and meningitis. There were 28 females and 82 males. Their ages ranged from 3 to 29, with a mean age of 12. All had been hospitalized at least six months, and most for at least three years. All had been vomiting six months or longer.

In the entire group, there were five patients who could be characterized as "ruminators". These are patients who voluntarily, through efforts of the tongue, esophagus and stomach, bring food back into the mouth after having swallowed it, re-chew it, and then swallow it again This procedure continues from one meal to the next, continuously during the entire waking period. The mechanism of this action is not understood, but resembles a reflex. It seems to be triggered by some pleasant acid taste of the gastric contents. Food is constantly lost, not because it is spat out but because a larger

quantity is brought up than can be held in the mouth or conveniently swallowed.

Previous therapy with tranquilizers, muscle relaxants and anticonvulsants had been common, and the results with these were available for purposes of comparison. Many patients had undergone long courses with chlorpromazine, reserpine or meprobamate. Trifluoperazine, perphenazine, prochlorperazine, and other potent phenothiazine derivatives had proved variably successful as tranquilizers, but had not stopped the vomiting. Alkaloids such as hyoscyamine, atropine, and others of the belladonna group had produced no change. Cyclizine, meclizine, dimenhydrinate and several other supposedly effective antinauseants had failed. Barbiturates and antihistamines likewise had been of no avail. In 5 patients (later to be described) surgical procedures had been carried out, but still the vomiting continued.

Before carphenazine was begun, all other therapeutic agents and procedures, except physiotherapy, psychotherapy and anticonvulsant medications, were withdrawn. Each patient was given a thorough physical and neurological examination, including blood cytology and urinalysis, and these were repeated at least once during treatment. As a check on possible potentiation of epilepsy, electroencephalograms were obtained on 5 patients before treatment and at several times later.

Dosage of carphenazine was individualized, but usually was started at one 12.5 mg. tablet three or four times a day. The lowest dosage was 6.25 mg. three times a day. Where indicated, the initial dosage was increased, although the usual dosage remained 12.5 mg. three or four times daily. In instances where the drug has produced good results, the patients are still being maintained at their optimal dosages.

Evaluation of results was based on objective observation of reduced (1) spasticity, (2) hyperactive, aggressive behavior, and (3) vomiting. These were all expressed as percentages.

RESULTS

The effect of carphenazine on vomiting was remarkable. Of 110 problem vomiters in the group, 102 were completely controlled after one or two doses, and began to gain weight at once. An additional patient was almost completely controlled (estimated at 99 per cent) and 2 more were judged to be about 75 per cent controlled.

These 105 included 68 persistent vomiters, 35 of them so gravely affected that life was threatened, and 37 of 42 acute vomiters. All had been in very poor condition because of a long-continued loss of weight and malnutrition. To be certain that the effect was due to carphenazine, the agent was temporarily withheld from a few patients. They returned to an occasional vomiting, which again disappeared when carphenazine was resumed. At present report, those being maintained on carphenazine have not vomited, and none have been given any other agent to control this difficulty (Table 1).

Table I. Effect of Carphenazine on 110 Brain-Damaged Spastics, Epileptics, and Mental Defectives in a State Training School

Problem	No. of Patients	Improvement or Control				
		Complete	75%–99%	25%–74%	Less than 25%	None
Vomiting, persistent (associated with brain damage)	68	65	3	0	0	0
Vomiting, acute (associated with infections)	42	37	0	0	0	5

Carphenazine also proved to be a good tranquilizer. To patients who had been hyperactive, aggressive, or extremely unstable emotionally, the compound was given in doses ranging from 6.25 mg. to 25 mg. every six hours. All were from 75 per cent to 100 per cent improved, becoming quieter, relaxed, and more cooperative. Very little oversedation was noted.

Neither the tonic nor athetoid spastic showed much improvement on carphenazine. Of 34 spastics treated, 16 showed a reduction of spasticity estimated to be between 15 per cent and 35 per cent; the other 18 were unchanged. The tonic type was benefited slightly more than the athetoid; in these, the estimate was between 25 per cent and 35 per cent improvement.

The electroencephalograms taken on 5 patients showed consistent strengthening of the alpha activity, with much better definition in all cases. The amplitude was much higher in all but 2, in which it was decreased. The frequency was decreased in 4. In all cases, the electroencephalograms tended toward normalization, with no epileptic or convulsive type patterns. This was in agreement with the reduction in seizures noted during treatment. Although this could be attributed to a lessening in tension in these patients rather than to any specific antiepileptic activity of carphenazine, it was nevertheless gratifying.

The blood studies and urinalyses showed no significant alterations. Blood cell counts and all physical and chemical values remained within normal limits throughout the study.

SIDE EFFECTS

No side effects resulted, other than an initial drowsiness, which disappeared after four or five days of therapy. Dosage was held constant during this initial phase, but could then be increased as needed, the maintenance dosage usually becoming stabilized at either 12.5 mg. or 25 mg. every six hours. However, some patients were given dosage as high as 75 mg. every six hours without untoward effects of any kind, unless the dosage was built up too rapidly. Extrapyramidal reactions or Parkinsonian effects did not appear at the dosage levels used.

The 5 ruminators were all in extremely poor condition when therapy was begun. All agents previously mentioned had been used, but nothing had seemed to curb this activity. Constant, small feedings had been tried, and also starvation by mouth. In an effort to preserve their lives, vagotomy had been performed on 2, gastrotomy on 1, and prefrontal lobotomy on all 5; but ruminating and loss of weight had continued. The case histories, briefly summarized, follow.

CASE REPORTS

Case 1. This 11-year-old girl, a mongoloid, had begun ruminating when hospitalized three years previously. Originally rather fat but well developed, her weight eventually had dropped to 18 pounds. In spite of the severe malnutrition, she had been quite aggressive and combative. Dosage of carphenazine was begun at 6.25 mg. every six hours. This slowed down her rumination but did not stop it. Dosage was then increased to 37.5 mg. every six hours, and at this level control was complete and has been satisfactorily maintained. Her weight has increased to 52 pounds. She is also much calmer and less aggressive.

Case 2. This 5-year-old boy, brain damaged at birth, had been admitted in very good physical condition two years previously. Originally well developed and well adjusted, he had begun a peculiar air-swallowing process two to three months after admission. About five months later he also had begun to ruminate in conjunction with this procedure. Because much food had been steadily lost, he had gone down to 21 pounds and was very seriously mal-

nourished. Carphenazine, 6.25 mg. exery six hours, was administered and this was slowly increased to 25 mg. every six hours. At this dosage, air swallowing continued but rumination was about 75 per cent controlled. His weight increased to 36 pounds, and he was in much better physical condition.

Case 3. This 13-year-old boy, with brain damage following encephalitis, had been admitted a year ago. He had begun vomiting two months after admission, and ruminating a month or two later. At first well developed, he rapidly had lost weight, dropping from 56 to 33 pounds in a few months. At start of therapy, he appeared starved, marasmic, and moribund. Initially given in a dose of 6.25 mg. every six hours, carphenazine was soon increased to 25 mg. every six hours. At this level, rumination gradually stopped, followed soon by vomiting. On maintenance at this dosage, the patient remained active and healthy, his weight going up to 68 pounds. In this case, as in the 2 following cases, there is little doubt that the medication was life saving.

Case 4. This 10-year-old boy, with a record of prenatal brain damage, had been hospitalized for two years before therapy with carphenazine. Although vomiting had begun soon after admission, it had not become a serious problem until he also had begun to ruminate. Then, in a period of less than nine months, his weight had fallen from 47 to 18 pounds. Vagotomy and prefrontal lobotomy both had been tried, but had produced no change. Dosage of carphenazine was then initiated at 12 5 mg. every six hours and was rapidly stepped up to 25 mg. every six hours. Regurgitation and rumination were completely controlled. His weight at time of this report is 47 pounds, and he is in good physical condition.

Case 5. This 18-year-old boy, brain damaged at birth, had been admitted 3 years previously. He had begun to vomit soon after admission, but had been able to maintain his weight at 51 pounds for a period of two and a half years. Approximately eight months before therapy with carphenazine, he had begun to regurgitate and ruminate very seriously. His weight had dropped to 27 pounds, and he had nearly died. Gastrotomy, vagotomy, and prefrontal lobotomy had been performed in an effort to save him. Prefrontal lobotomy had had some effect, but he had not gained weight. He simply had stopped losing weight, maintaining himself in an extremely emaciated condition at 27 pounds. Carphenazine was started at 25 mg. every six hours, and was increased the third day

to 37.5 mg. every six hours. At this level, rumination was about 75 per cent controlled, but the patient was much too deeply sedated. For several weeks the dosage had to be greatly reduced, but then could be slowly built up again. Maintenance at 62.5 mg. every six hours has, at the time of the present report, allowed an estimated 99 per cent control of this severe symptom. Although the patient occasionally still ruminates, he now weighs 102 pounds and is in excellent physical condition.

ADDITIONAL INTERESTING CASES

One 18-year-old girl had scratched herself constantly for over eight years. This had kept her skin irritated and abraded, and there was a rash over most of her body. Many drugs, including antihistamines, had been prescribed for this neurodermatitis, but it had resisted all previous therapy. Carphenazine, 6.25 mg. every eight hours, was given for six weeks and then increased to 12.5 mg. every eight hours. The patient responded completely, and for the first time it was possible to release her hands without her scratching herself. The rash disappeared, and she became comfortable as long as the agent was continued. When it was tentatively stopped, the rash and itching came back.

In another case, a 29-year-old man, a mongoloid, had been treated for both vomiting and self-mutilation. For most of his life he had been beating himself, and was constantly bruised about the face. He had been extremely hyperactive, although all of this excess activity was directed against himself. Many psychopharmacologic agents had been tried, including reserpine and chlorpromazine, all with no effect. Carphenazine in doses of 12.5 mg. every four hours was given, and this kept him about 50 per cent calmer. His vomiting was also about 75 per cent controlled.

SUMMARY AND CONCLUSIONS

In a study involving 110 problem vomiters in a state school for mental defectives, carphenazine was extremely effective. Control of vomiting was complete and immediate in 102, with three others at least 75 per cent controlled. Vomiting in 68 of these had been associated with brain damage, and in 35 was sufficiently severe and persistent to threaten life because of loss of weight and malnutrition. Of 42 acute vomiters, 37 were also fully controlled. Dosage was usually 6.25 mg or 12.5 mg., administered as ½ or 1 tablet three or four times daily. No other agent or procedure had been effective.

There were no side effects, other than an initial transient drowsi-

ness, and no extrapyramidal symptoms. All values in blood studies and urinalyses were within normal limits, and electroencephalograms showed no potentiation of epilepsy.

Carphenazine also proved to be a potent tranquilizer, with an estimated 75 per cent to 100 per cent calming effect in hyperactive patients. Relaxation of spasticity was low, only about 25 per cent in about half the tonic or athetoid types.

Carphenazine is a potent tranquilizer and an exceptionally effective antiemetic agent.

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Activities of The Poison Control Center . . .

TURPENTINE POISONING

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TURPENTINE is an oleoresin a derivative of the various species of Pinus. It has a characteristic odor and taste. Turpentine oil or spirits of turpentine is manufactured by the steam distillation of the sticky resinous secretion. The mixture varies considerably in composition, since it consists of a variety of terpenes, pinene, dipentene, sylvestrene and a host of other minor constituents. The chief ingredient however is a-pinene. The distillate is colorless and has a characteristic odor and taste. The odor is perhaps due to the peroxides which are formed in the solution by autoxidation in air. Turpentine oil is almost insoluble in water but it will enter in a mixture with alcohol and ether. It is a good solvent and used in large quantities by the paint and varnish industry for mixing paints and removing paint stains. It is also used in shoe polish and leather dressings, polishes and waxes. A considerable amount is also used in pharmaceuticals and chemicals for "stupes" externally for "rheumatic pains" and internally in the treatment of parasitic infestations, as an expectorant and as an abortifacient. Because of its widespread use in industry it is readily available practically in every home often not in its original container and within easy reach of unsuspecting children.

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Toxic effects: Both local and systemic manifestations have been reported. Turpentine is quickly absorbed from the skin, gastrointestinal and respiratory tracts. As little as 15 ml. (one swallow) may cause a fatality in a child. The lethal dose for adults is estimated to range between 4-6 ounces. (We have had children who swallowed between 2-3 ounces and who survived). Turpentine is a marked irritant and its absorption is reported to have a damaging effect on the kidneys. Nephritis may also occur from chronic exposure due to the inhalation of turpentine vapor. A higher incidence of nephritis has been observed in painters.

Some investigators believe that neither turpentine nor paint fumes are renal irritants and do not cause glomerulonephritis in the human kidney. (In our series of 450 cases of accidental ingestions, kidney damage was not reported). The maximum allowable concentration value of turpentine parts per million of air is 100 parts per million. In higher concentrations the inhalation of turpentine vapor may cause hyperpnea, vertigo, tachycardia, bronchitis, convulsions and central nervous system disturbances and nephritis.

When applied to the skin as a rubifacient it may cause redness, itching, warmth, blisters, pain, smarting and burns. The vesication after blistering heals rather slowly. When turpentine gets into contact with the eyes it may cause a conjunctivitis, edema of the lids and blepharospasm. When taken internally the most common symptoms are burning in the mouth and throat, esophagus and stomach, abdominal pains, colic and diarrhea, fever and rapid and thready pulse. Dyspnea, cyanosis and clammy skin are not uncommon. In severe cases, excitement, delirium, headache, ataxia, vertigo, giddiness, stupor, convulsions and coma may also occur. Respirations may become slow and a broncho-pneumonia and pulmonary edema may also develop. The pupils may become dilated and non-reactive. There may also be painful urination, hematuria, albuminuria and a glycosuria due to the affection of the kidneys. In terminal cases death is due to respiratory failure. The characteristic odor of turpentine is usually present on the breath and in the vomitus.

Treatment consists of rapid evacuation by dilution and elimination of the toxic material. It consists of gastric lavage with tap water, saline or sodium bicarbonate. Care should be exercised to avoid aspiration. Saline cathartics with sodium or magnesium sulfate and large amounts of fluids are administered by mouth to

promote diuresis. It is also advisable to use demulcents such as milk and egg white. Morphine and its derivatives should not be administered in order not to aggravate the possible respiratory depression but sedation may be needed for pain. In case of severe depression stimulants such as caffeine, sodium benzoate may be helpful. Exchange transfusions have also been used. In the main the treatment is chiefly symptomatic and supportive. For first aid a tablespoon of salt in a glass of warm water and repeated until vomitus is clear is recommended. Two teaspoons of baking soda in a glass of water may be given. One to two glasses of water or milk are good first aid measures until the physician arrives. The best treatment however is *total prevention*. The U. S. Food and Drug Administration has wisely declared turpentine a hazardous substance that requires a special label to protect the public health and safety. While labelling is important we cannot rely on this measure alone to eliminate poisonings. Regulations must be coupled with *education*. Physicians must alert parents on the danger of products containing turpentine and advise them to keep them in their original container, securely stored away.

Turpentine Poisonings*
New York City Department of Health
Poison Control Center 1955-61**

Reported Occurences by Year	Under 1 Year	(1 - 2)	(3 - 4)	(5 - 9)	(10-14)	(15-20)	21	Total
	AGE IN YEARS							
	NUMBER OF INCIDENTS							
1955	0	18	0	3	0	2	4	27
1956	0	29	4	2	0	4	10	49
1957	0	49	5	1	0	7	13	75
1958	17	31	8	2	0	4	5	67
1959	5	58	7	3	1	6	10	90
1960	19	40	12	4	2	3	9	89
1961	3	31	9	1	0	1	3	48
Total	44	256	45	16	3	27	54	445

* Includes only poisonings where turpentine was reported specifically as the offending agent and does not include incidents due to paint, paint-thinners, varnishes or polishes.

**From March 9, 1955 to July 1961.

Of the total number of incidents, 77.5% occurred in children under 5 years of age. The increase in the number of poisonings in the 15-year and over group is due perhaps to intentional poisonings, the agent being used in attempted suicides. In this series no fatalities were reported, though one fatality occurred in a two year old female child who ingested 15 ml. of a Benzene-Turpentine mixture. The painter who recently painted the apartment left the

mixture in a small bottle outside the kitchen window sill. The victim obtained it and drank a portion of its contents. The only way the mother learned about the incident was because of the odor. The child's stomach was lavaged within an hour with sodium bicarbonate and she was also given mineral oil and treated symptomatically. In spite of appropriate therapy including oxygen and stimulants the child developed convulsions, became comatose and died on the day of admission.

It is also of interest that our series of 445 non-fatal cases do not include any cases with evident kidney damage. This may be due to the prompt and appropriate treatment which was administered to these patients.

The most recent 70 cases reported were subjected to a statistical analysis and the findings are as follows:

Variation by Sex:

	Number	Per Cent
Male	47	67.1
Female	23	32.9
Total	70	100.0

A marked male preponderance is noted.

Distribution by Age in Years:

Age	Number	Per Cent
0	5	7.1
1	35	50.0
2	21	30.0
3	5	7.1
4	1	1.4
5 and over	3*	4.4
Total	70	100.0

Eighty percent of occurrences were at ages one and two years.
*Includes one 16 year old and two 18 year olds.

Dosage: The average dose was 15 cc. There were some who ingested unknown quantities and a few who ingested from 2-3 ounces.

Original Container:	Number	Per Cent
Yes	24	34.3
No	30	42.8
Unknown	16	22.9
	70	100.0

Of the incidents in which the type of container was known in 55.6% the offending agent was *not* in the original container.

In all instances where the location of the offending agent was known, the kitchen was the place of occurrence.

Manifestation of Symptoms:	Number	Per Cent
Yes	42	60.0
No	18	25.7
Unknown	10	14.3
	70	100.0

In 25.7 of the cases the patients were known to be symptom-free.

*Symptoms and Signs of Turpentine Poisoning:**

Frequency of Symptoms	Number
Burning in Mouth and Throat	22
Vomiting	15
Dyspnea	13
Coughing and Choking	9
Nausea	8
Abdominal Pain	7
Cyanosis	5
Stupor	4
Coma	3
Diarrhea	2
Convulsions	1
Fever	1

*Some patients manifested more than one symptom.

The most common symptom noted was burning in mouth and throat and reported in almost one-third of the cases studied. Dyspnea was reported in 19% of the cases and 13% suffered from coughing and choking spells.

Treatment Agency:

	Number	Per Cent
In-Patient Dept. Care	37	52.9
Hospital Emergency Room only	26	37.1
Private Physician only	4	5.7
In-Patient and Out-Patient Care	2	2.9
Unknown	1	1.4
	70	100.0

Ninety-three percent of the patients received treatment at a hospital either in the emergency room, out-patient and in the in-patient services.

Hospital Stay (In-patient):

Days Care	Number of Patients	Per Cent
Under one day	4	10.2
One day	9	23.1
2	3	7.7
3	9	23.1
4	2	5.1
5	3	7.7
6	3	7.7
7	3	7.7
8	3	7.7
	39	100.0

The average length of stay was from 1-4 days. Nearly 31% of the patients hospitalized, required 5-8 days of hospital care.

Type of Treatment:

	Yes	No	Unknown	Total
Lavage	48	13	9	70
Vomiting (induced)	22	18	30	70

Of the patients in whom type of treatment was specified, 79% were treated with lavage and 55% of the patients where type of treatment was known, were treated with induced vomiting. In addition to lavage and induced vomiting some patients also received oxygen and antibiotic therapy. Symptomatic and supportive therapy were also administered. In the home some patients received milk as a first aid measure.

Other Characteristics: All the children studied were judged by their parents and the interviewing public health nurse to be of average growth and development and of normal intelligence. They were characterized by their parents as curious and some as mischievous. Only 5 were previously involved in accidental occurences. The socio-economic level was classed as "average" in over 70% of the cases.

Preventability: The public health nurse and one of the authors (Harold Jacobziner, M.D.) after a careful review of each case, judged all above incidents as "preventable".

CASE REPORTS

It may be well to cite a few examples (case reports) which illustrate the mode of occurrence in accidental ingestions of turpentine.

Case 1: A 13 month old male child ingested 1-2 ounces of the product. Family was in the process of painting the apartment. Turpentine was placed under the kitchen sink in a mayonnaise jar. When the toddler was left alone for a few seconds he removed the jar, opened it and swallowed some of its contents. When mother returned to the kitchen she found the child in the process of swallowing the turpentine from the jar. She rushed the child immediately to the hospital where the stomach was lavaged. The child was hospitalized for two days and was discharged following a complete recovery.

Case 2: This 18 month old male infant was under the care of a neighbor in the absence of his mother. An older sibling started a small kitchen fire while playing with matches. In the excitement, the child drank some turpentine which he obtained on the kitchen floor where it was left by the neighbor who used it to remove some paint from a piece of furniture. The episode occurred while the neighbor's back was turned for a moment. When the mother

returned she noted a burn on child's face around the mouth and the odor of turpentine was on his breath. The child was taken to a hospital. His stomach was lavaged with milk and water and after 3 days of hospitalization, made a complete recovery.

Case 3: Father was painting the kitchen and used some turpentine. Mother placed the can on the stove and went out to hang some clothes in the backyard taking the child with her. The child returned to the kitchen unnoticed by the mother. He retrieved the can from the stove and ingested 1-2 teaspoons of turpentine. He had burning in the mouth and throat, abdominal pains, vomiting and dyspnea. He was taken to a nearby hospital where vomiting was induced. The patient was also given milk and lemons and observed for 24 hours prior to discharge after he became symptom free.

Case 4: This 2½ year old male child was left alone in the kitchen playing with toys while mother was cleaning up the bedroom. The child obtained a glass of turpentine on the floor which was left by the painter the previous day and apparently drank some of the contents. Upon her return to the kitchen she found the child gasping and rolling on the floor. The child's breath had the characteristic odor of turpentine. The mother then realized what happened and took the child to a hospital emergency room where the stomach was lavaged and supportive therapy administered. He remained in the hospital for 2 days.

Case 5: Mother placed turpentine in an apple cider bottle and left the contents on a kitchen table. This 16 year old patient was thirsty and mistakenly drank the turpentine. She could not smell the turpentine because of a "stuffy nose". The presenting symptoms on admission to the hospital were burning in the mouth and throat, abdominal pains, nausea, vomiting and dyspnea. Patient was lavaged within one hour following ingestion. Patient had to be hospitalized for 6 days and given symptomatic and supportive therapy before she became symptom free.

Case 6: Mother related to the public health nurse who visited the home that her husband was painting the apartment in his spare time. He put paints and turpentine in the foyer. Mother heard this two-year-old female child crying out and chocking. An investigation revealed that child was inhaling turpentine fumes. Patient was immediately taken to Bellevue Hospital. On admission to the hospital child had burning in mouth and throat, choking and vomiting. The blood count showed a hemoglobin of 11 grams and

the red blood count was 3,800,000. The leucocyte count was 14,400 with 60% polys, 12% bands and 28% lymphocytes.

The child's stomach was lavaged within 30 minutes following ingestion and 60 cc of mineral oil were also given following lavage. Child remained in the hospital for six days.

Case 7: While mother was busy caring for an infant sibling this 1½-year-old male child went into the bathroom and found a "*coke*" bottle which contained about "1 inch" of turpentine and swallowed an estimated "1 ounce". He was taken to a hospital where the stomach was lavaged within 35 minutes. He was also given one ounce of mineral oil following ingestion. On admission patient had nausea and cyanosis. After treatment in the emergency room patient was apparently improved and was sent home. He developed a temperature and was again taken to the hospital and admitted to the in-patient service where he remained for 5 days. He was given penicillin, and supportive therapy and completely recovered.

Case 8: The family moved into a new two room apartment which they were in process of redecorating. This 16 month old female child had some paint marks on her face and mother removed them with turpentine. The mother left the contained with the cap off on a low table in the bedroom. While the mother went into the other room for a moment the child obtained the can and swallowed "1 large gulp" of the contents. The patient had burning in mouth and throat, nausea, dyspnea, cough and also developed a diarrhea one day following ingestion. An X-ray was taken and did not show any pulmonary pathology. After several hours of observation in the emergency room child became symptom free. She was sent home with instructions to return immediately if any symptoms recur. According to the mother the child was well in a few days.

Case 9: This two year old male child while visiting grandmother found a bottle containing turpentine on a dresser table in the bedroom. He was taken to a nearby hospital where he was first treated in the emergency room. His stomach was lavaged with milk within 1 hour following ingestion and he was sent home. Patient continued to cough and also developed a temperature. He was readmitted to another hospital where a diagnosis of pneumonia was made. Patient remained in this hospital for eight days and made a full recovery.

Grateful acknowledgment is expressed to Mr. Roland Merchant and Mr. Clifford Hamburger for aid in collating statistical data.

125 *Worth Street, New York* 13

(*This is the eleventh of a series of papers by Dr. Jacobziner*)

Pediatric Conference . . .

CASE PRESENTATIONS FROM PEDIATRIC DEPARTMENT,
MISERICORDIA HOSPITAL, BRONX, NEW YORK,
VINCENT P. CASEY, M.D., *Director*

Biliary Atresia . . . Recurrent Craniopharyngioma—Part I[*]
PRESENTED BEFORE BRONX PEDIATRIC SOCIETY AT
MORRISANIA HOSPITAL AUDITORIUM—MARCH 8, 1961

Discussors: C. JOSEPH DELANEY, M.D., *Attending Surgeon*
JAMES T. DANIELS, M.D., *Chief Neuro-Surgeon*
HARRY BUCALO, M.D., *Director of Pathology*
CESARE E. CUCCI, M.D., *Asst. Att. Pediatric Cardiologist . . .*
All at Misericordia Hospital

DR. GOLDFARB: The following presentation of cases from the pediatric department of Misericordia Hospital will, for the scientific session, be presided over by Dr. Charles Fried, an attending on the service. Dr. Fried. . .

DR. FRIED: Dr. Casey has asked me to express his profound regrets at being unable to attend this first meeting of the Misericordia group. The program as printed will be a little changed and Biliary Atresia, case number three will be presented first. This will be presented by Dr. Shapiro and discussed by Dr. C. J. Delaney, who is our attending surgeon. Dr. Shapiro . . .

DR. SHAPIRO: This is the first hospital admission of a 7-week old white male infant with a chief complaint of jaundice of 6 weeks' duration. The mother stated she thought the baby looked yellowish when she returned home. When the infant was about two weeks old, she noted the abdomen appeared full. The baby's stools then appeared to become lighter in color and the urine stained the diaper deeply.

The mother continued to give routine care over the next several weeks. During this time she noted gradual enlargement of the abdomen; however, there was no vomiting. The infant took his formula well. The bowel movements were normal except for the color. The child appeared happy and in no apparent distress. At this time pediatric consultation was advised. The pediatric consultant advised hospitalization.

Birth History: Full-term, spontaneous delivery, birth weight 8 lbs. 1½ oz. The ante-natal care was entirely uneventful. There

[*] The Biliary Atresia and Recurrent Craniopharyngioma Case Reports here presented are two of four discussed at the Meeting recorded. The October issue will present the third and fourth cases: Cytomegalic Inclusion and Rheumatic Fever.

were no abnormalities noted at birth and post-partum course was normal. Family history was non-contributory. Physical examination disclosed a well-nourished, white male infant who was playful, alert and afebrile, weight was 12 lbs., 1½ oz., length 21", head circumference 13¾", abdominal circumference 19". The skin had good turgor and appeared yellowish-white. The head, neck, and thorax were not remarkable. Heart and lungs were normal. The extremities and neurological examination were negative. The eyes showed icteric sclerae and the fundi were negative. The abdomen appeared markedly distended. The superficial skin veins were prominent. The liver appeared huge, its edge being 6 fingers below the costal margin. It was non-tender and hard. The edge was smooth and firm. There were no masses or areas of tenderness noted. Rectal examination was negative. The penis showed hypospadias.

The initial laboratory work-up disclosed the following: Hematocrit 35%, WBC 10.250 with 37 Polys 67 Lymphs, 1 band, 2 eosimophile, 1 basophile, Reticulocytes 1.7%, Bleeding Time 2'20", Coagulation Time 2'45", Total Bilirubin 4.8 mg%, Indirect 4.6 mg%, Direct 0.2 mg%, Thymol Turbidity 2.1 units, Total protein 7 mgs., albumin 5.5, globulin 1.5. Cephalin Flocculation 24 and 48 hours was negative, Cholesterol 248 mgs. SGDT transaminase 196. Both direct and indirect Coombs test was negative, child was group A, Rt. and Pos. Prothrombin time undiluted 15 sec. 100% Control 15 sec. 100%, urine clear, acid negative for albumin, sugar microscopic, urobilinogen negative. Tests on urine showed no inclusion bodies. Stools were negative for urobilinogen. X-rays of the skull were negative.

Course while in the hospital: Infant was operated on by Dr. C. J. Delaney on the 6th hospital day. He found on opening the abdomen a moderate amount of bile-colored fluid. The abdominal organs were covered with bile-stained fluid. The liver was 3 times normal size and hobnail in appearance. The hepato-duodenal ligament revealed no evidence of a biliary tree. There was a small nubbin of the hepatic duct entrance on the surface of the liver at the porta hepatis. This showed no bulge but a definite atresia at this point. The surgical aspects will be discussed by Dr. Delaney.

Post-operatively, the child ran a septic, toxic course. Fluid balance and blood integrity were maintained. Four days post-operatively, fluid from a Levine tube was shown to be free of bile and Gmelin's and Smith's tests were negative. The urine was now

positive for bile but negative for urobilinogen. The total bilirubin rose to 12.8 milligrams, 6.6 direct. At discharge the total bilirubin remained at 11 milligrams percent. The stool remained negative for bile. The child did well at home with no apparent symptoms. He ate well and stools appeared light yellow in color. His abdominal distention and jaundice remained. At five months, he developed high temperature and was readmitted. The examination disclosed a markedly icteric infant with marked abdominal distention. The positive findings now were evidence of pneumonitis, liver 6 fingers below the costal margin, and evidence of ascites. The total bilirubin was 6.6 with 2.6 direct and 4 milligram percent indirect. Total protein was 8.2, albumin 4.2, globulin 4, BUN 27, hemoglobin 5.4, and WBC 18,650 with 55 polys and 38 lymphs. Stools were positive for bile. X-ray of the chest disclosed bronchopneumonia. Nose and throat culture revealed non-hemolytic Aerobacter.

The infant ran a septic, downhill course with increasing dyspnea and cyanosis, and in spite of all supportive measures, expired on the 19th hospital day.

DR. DELANEY: I was to discuss the operative findings and I don't want to bore you too much, but in a few words, I'll tell you what was found. On opening the abdomen, we found a very large liver, hard in character, occupying a large part of the right side of the abdomen, relative to the other side. We explored the sub-hepatic area and found what we thought was a remnant of the gallbladder. It had no lobe, contained no bile and it was a very rudimentary structure that we assumed was probably gallbladder. Exploration of the hepato-duodenal ligament which takes about 3 hours to do—it's a very long, tedious and careful procedure—revealed no evidence of a biliary tree whatsoever. At the porta hepatis just above the duodenal ligament, I found a small nubbin, maybe 1 cm. in diameter, and it wasn't bulging but I assumed that probably it was the entrance to the hepatic duct. I put a needle in it and got no bile from it. Then, still feeling that that was probably the duct, I did a fish-mouth incision and dropped the anterior lip backwards, and when I did this, a small amount of bile showed and began to stain the area. The question then was what to do. First, I tried to pass a catheter and I couldn't do anything there, I couldn't get into the liver substance, and then I passed a probe up about a centimeter and a half and got blood so I decided to stop; then the question was what to do from there, and I thought I could plan to do a hepato-duodenostomy.

The child was not doing well. This was about 3½ hours after we began and the anaesthesist said he thought we ought to wait a little while, so rather than take a long time and mobilize the duodenum, I brought up the jejunum and did a hepato-jejunostomy. This procedure isn't ideal. It's something to do but we don't claim it's the ideal thing to do. The child ran a very septic temperature afterwards. We took x-rays showing that the anastomosis was working all right anatomically. How much bile was being passed into the gastro-intestinal tract was a question. Some of the tests showed bile and some of them showed no bile. Now, I think it could mean two things: first, that the urine might be staining the feces and the other, that the flow was intermittent and small in quantity.

The child, however, after the septic course was over did quite well, seemed to pick up, clinically the jaundice was less, started to eat, so we sent him home; then, as you know, while he was home, in the fifth month, he developed bronchopneumonia, but it had all the appearance to me of being a final picture of cirrhosis. He had marked ascites. I did two taps on this baby and got out large amounts of fluid. He went downhill rapidly which is the course of children of this type.

Now, I'll go on from there to discuss biliary cirrhosis, biliary atresia in general. The big problem in this, from a pediatrician's standpoint, is to make the diagnosis. I don't have to tell you that. The large number of cases of neonatal hepatitis is confusing, and all of the tests that have been done: the biopsy, the needle biopsy, the wedge biopsy, are not too clear. When you get it out, you can't tell from the biopsy in most cases whether you're dealing with an atresia or with a hepatitis. Consequently, you're left with the problem of making the diagnosis and waiting too long before you start the surgery.

The next factor is the type of treatment. It all depends on what type of atresia you have. If you have a tree in which the atresia is in the common duct or the hepatic duct where you can make an anastomosis, and you do it early enough, then you have a reasonable chance of getting a child well, but if you wait for a long period of time (now it was over 3-4 weeks) and the cirrhosis is bad, or you haven't anything to work with, then the case is pretty hopeless. There are some cases reported who lived to 14-15 years of age, and we have some who lived almost that long where nothing was done for them, but most of them die with a chronic cirrhosis.

An interesting thing happened while this baby was in the hospital. I got a letter from a doctor in Philadelphia saying that The Society for the Study of Biliary Atresia, was interested in the case. So I sent them a resume of the case, and they wrote back and said they would like to advise what to do if I gave them more data. I gave them more data and the next time I heard from them, the baby had died, but what they're doing down there is interesting. This has been in all the papers the last year. They're putting in these plastic tubes—either a tree of tubes, that is a framework, or one or two—into the substance of the liver, producing a fistula and then connecting this up with the gastrointestinal tract. I thought you might be interested in the correspondence on this case to a degree. This is a letter from Dr. Sterling who is apparently the doctor in charge of this group. It's the Einstein Clinic down there. It says: "Thank you very much for your letter concerning the child; I would be interested in knowing the status of the youngster's laboratory findings at this time. I am also interested in level serum proteins, albumin, blood ratio. We have had some degree of optimistic results in babies for whom we have used artificial bile ducts. I would be pleased to discuss this further with you . . ."

I wrote Dr. Sterling my thinking on this. I said: "I received your letter of December 29th including your reprint of artificial bile ducts. I'm sorry to report to you that the child about whom you wrote passed away last week. The cause of death was a progressive cirrhosis of the liver with ascites. It is interesting to note that right up until death, following the hepato-jejunostomy some bile was found in the intestinal tract. I think the work you are doing at the Albert Einstein Medical Center relative to congenital atresia is much to be complimented; however, we feel that before anything can be gained by the establishment of bile drainage in these cases, some method of early diagnosis in this is most important. I'm very happy to hear of any new modalities.

Now, he at the same time sent me a report of the cases that they have been doing there in the past few years, and this will give you an idea of the results generally. This is the picture of atresia throughout the country. They had 51 cases. I'll read the survey of the statistics: four of the 7 babies who had an external fistula established, died within 11 days after operation; the other 3 survived only 6-24 months. Bile was noted to drain from the liver in 5 infants; bile drainage did not continue after 2-4 months in 3 of the babies. Two of 4 babies in whom gallbladder-liver fistula

was established, died within 2 months postoperatively. The other 2 have survived thus far from 7 to 36 months. Bile was present in every one of these babies' bowel movements and has persisted in the two who are still alive. Seventeen babies had an intestinal pouch and a hepto-enteric fistula. Bile is present in the stools of 3 of 6 babies who are still alive. In babies who did not survive the operation 6 hours to 8 months, bile in the intestinal content was present in 6, intermittent in 3, and absent in 2.

The only reason I'm bringing that up is this: that bile in the stool is not significant of a successful operation. In these children, if they have an opening that's large enough to produce a normal drainage of the liver bed, that's one thing, but most of these no matter what modality you use, whether you use a duodenal or hepato-duodenostomy, putting drains into the liver, the drainage is very moderate and these children live anywhere from a few weeks to a few months and occasionally a few years, but they all eventually die of cirrhosis. Are there any questions?

DR. DELANEY: Until we can find a method of diagnosing these children after the second or third week, I don't think there's any hope of doing anything before that. In all of the biopsies, I think, as Dr. Bucalo will tell you, the presence of giant cells, enlargement of the cells lining the ducts, you get the appearance of both in both atresia, and in hepatitis.

QUESTION: What about cholangiography?

DR. DELANEY: This is very important. It saves you all the trouble of looking for the hepato-duodenal ligament. The only time you can use cholangiography is where you have a gallbladder. If you find a gallbladder, then you can put diodrast in the gallbladder and pump it into the ducts, and you can see where your atresia ends or whether or not you have an atresia.

QUESTION: What about an intravenous route?

DR. DELANEY: It has not been successful. There's been no way of doing that.

QUESTION: Was there any occasion during the operation on this baby for a liver biopsy?

DR. DELANEY: No, Dr. Casey asked me to try to get this baby back alive, and the diagnosis of cirrhosis was so definite. If there were a question, I would have done it, but here was a great big hobnail liver, and I think that would be just adding insult to injury in that case.

QUESTION: Dr. Delaney, if you remember, it used to be that when a mother reported her baby jaundiced at 3 weeks, we'd take x-rays and send him home. I recall a few years ago, a controversy appeared in the literature concerning whether it was better to operate early on the child who was jaundiced, to make a differential diagnosis, or better to wait, and Boston Children's reported a fairly high morbidity and mortality, and got over the idea it was better to do it early. For those who don't know, the people of Boston have changed their mind, like most pediatric surgeons, and we should be aware cirrhosis does begin quite early and it should be found early. I think early diagnosis is based highly on suspicion and a quick look may be very helpful. I mean you should go in if you're going to save that liver once jaundice occurs, and we do it much earlier than was originally thought.

DR. DELANEY: That's right. There was a report from Boston, showing only 7 cases in which they did wedge biopsies. I think they had 7 deaths, so the danger of doing a laparotomy, even though you do it under local anaesthesia and take a wedge out in a case that's a serum hepatitis or infectious hepatitis, is not without its dangers; and believe me, a pediatrician who tells a mother after 2 weeks "we'd better do a biopsy of this baby, it may have an atresia," has to think. It's an easy procedure but the morbidity and the mortality is very high.

QUESTION: Do you think it's possible to make the diagnosis without operation?

DR. DELANEY: You have to have something to inject. If you have a patent gallbladder or you have a gallbladder even that contains some bile, you can at least outline the ductal system. Other than that (in this case of mine there was nothing to inject), you would just have to go in and pick what would be the hepatic duct, the portal vein and the hepatic artery, which run along the hepato-duodenal ligament.

QUESTION: You referred to the fact, Dr. Delaney, that there was some bile in the stool. I think we must remember we don't understand everything about bile stains yet, but enough to know that one doesn't have to have a patent gallbladder and a patent biliary tree to find bile staining and coloration of the stool.

DR. DELANEY: Well, in most cases, or in a great many cases, a stool is stained by the urine in an infant and gives you a false impression. Practically everybody tells you that all stool examinations should be done within the rectum not out of the diaper, but it

is very true there is a certain amount of bile found intermittently In all reports, they state bile is found in a great many cases, and yet we know there isn't a great deal of function left in those anastomoses. Unfortunately, that happens to be the truth. Another fact is this: in some of these cases, they have an intra-hepatic obstruction in which the cells lining the ducts are enlarged, hypertrophied, or hypoplastic, and there's no bile excreted into the ducts —the intrahepatic ducts.

QUESTION: These figures on bilirubin determination are a little confusing. We had a case recently where I had a total bilirubin of about 9, a direct of about 5, and indirectly, STO was elevated, and the stool was yellow. We watched this child over a period and couldn't make up our minds. Right now the child is doing very well and the thing has cleared. From these figures, for instance, a direct of 4.6, 3.5 with a total atresia, it seems awfully peculiar to me.

QUESTION: This is before the operation?

DR. LUPARO: I have seen in every case, regardless of the figures, indication of obstruction, and the danger of doing liver puncture, wedge biopsy, is all something to think about. Every case has to be individualized, and you just can't go in and operate on every child after 2, 3, 4 weeks.

DR. DELANEY: That's right. Of course, there are some of these that are operated on and reported as atretic and then 4-5 weeks later, they are perfectly normal children, which means that the bile tree was missed and that is a possibility, in spite of the fact it was done by very excellent surgeons. Then, of course, we have the case of the inspisated bile as they call it—the erythroblastosis cases and that type—but I don't think they're to be considered in the same breath with an atresia because they get better whether you open them and dilate them and wash them out with saline, or don't do anything. They seem to clear up after a reasonable length of time, but to conclude, I'd like to quote Dr. Potts of Chicago, for whom I have the greatest respect, who says "atresia is the darkest chapter in pediatric surgery, atresia of the biliary system". And I think it's true. Until we can find some method of determining at a reasonable time that these children have an atresia, and then, once we have done it, develop a method that is going to be technically a good method, I don't think that hepatoduodenotomy, or hepato-jejunostomy is an ideal method in a very small infant.

If you can find just something to form a duct, if you had 2 cm. or 1½ cm. of hepatic duct, something to put a catheter in, you may be successful; if you can't put a catheter in any of these holes, believe me, you're heading for an unsuccessful procedure.

The second case on the program will be: "Recurrent Craniopharyngioma". The case will be presented by Dr. Ante.

DR. ANTE: On May 9, 1957, at age 4, this female child was referred for neurosurgical study because of failing vision, increasingly severe, generalized headache and weakness, polydipsia and polyuria. Neurological examination revealed a bitemporal hemianopsia, primary optic atrophy, more marked on the right side, with reduction of visual acuity, more marked in the right eye. Slight obesity suggestive of a Froelich was observed. The skin was dry. Radiographic examination of the skull revealed a symmetrically enlarged sella turcia containing a rather dense calcification. There were no other calcifications present within the cranium. Pneumoencephalograph was performed and followed by craniotomy on May 29, 1957. At operation a cystic intracellar mass was found displacing the optic chiasm upward with greater elevation on the right side, thus raising the right optic nerve more than the left. After a satisfactory post-operative course the child was discharged on June 9, 1957.

During the subsequent three years, the child returned to school, performing her school work fairly well with occasional episodes of headache. The polydipsia and polyuria continued. She was not disturbed by her visual deficit. On October 17, 1959, her physician in Honesdale, Pennsylvania, reported that the child had been hospitalized because of weakness and projectile vomiting. He was "impressed by her skin being dry and lack of evidence of developing secondary sex characteristics". A serum sodium of 128 milliequivalents was found and she was placed on hydrocortisone, 10 mgms. t.i.d and thyroid. The vomiting promptly subsided and her lassitide gradually decreased. This improvement was maintained until November 11, 1960, when her physician again reported the abrupt onset of severe headache and projectile vomiting. She returned to New York and was admitted to Misericordia Hospital on November 16, 1960. On examination she was found to have lost practically all vision in the right eye; the left temporal hemianopsia was present, and the optic atrophy had advanced. She had become more obese, the polydipsia, polyuria and dryness of

the skin, were even more marked than previously. On November 23, 1960, the second craniotomy was performed and a large recurrence of the mass was encountered. There was a large supra-sellar extension of the neoplasm encountered, over which the optic chiasm was stretched, and the right optic nerve was flattened, ribbon-like, over the antero-lateral aspect of the mass. The child responded well and was discharged from the hospital on December 6, 1960. The neoplasm was again identified as a craniopharyngioma.

DR. FRIED: This case will be discussed by Dr. James Daniels, Chief of Neuro-Surgery of Misericordia Hospital and Assistant Professor of Neuro-Surgery at the N.Y.U. Medical School.

DR. DANIELS: Like Dr. Delaney, I must express my appreciation for the invitation to appear before The Bronx County Pediatric Society. I'm equally pleased, as Dr. Delaney is, and grateful for this opportunity to discuss this case of a 9-year old child, rather than a 4-year old child, as the protocol indicates, when she was first seen in May, 1957, at the Manhattan Eye and Ear Hospital in New York City, and through the courtesy of Dr. Byron Smith, I was asked to see her. The child had been admitted, as the protocol indicates, because of the manifestations enumerated and indicated, and at that time Dr. Smith found a bitemporal hemianopsia in a somewhat obese child with headache and oddly enough very little pre-occupation with the visual difficulty.

(Showing films—Plain X-ray of the skull, lateral view): This lateral film, as you see, demonstrates a ballooning of the sella which is symmetrically and rather markedly enlarged, as a matter of fact, with this intrasellar calcification. The stereoscopic views demonstrate that this calcification is within the sella and not situated para-sellar; a pneumoencephalogram done at the time of the first admission showing somewhat enlarged lateral ventricles, symmetrically enlarged, and slightly enlarged third ventricles.

We were much concerned with the findings in this lateral view. The lateral ventricles are unremarkable actually, but knowing and suspecting a craniopharyngioma, and knowing the tendency rather frequently to extend above the sella, we interpreted this area of contrast as being the superior portion of the third ventricle and wondered whether this represented a large, tremendous, supra-sellar extension of the neoplasm from the sella proper.

The postero-anterior view in the pneumoencephalogram added nothing to this information.

These are the visual fields taken at about the time of the first operation, but after the child had been transferred from the Manhattan Eye and Ear. These fields were done by Dr. Byron Smith who had previously found a bitemporal hemianopsia, but with a greater encroachment on both the inferior and superior nasal fields on the right side.

Now, the child had a rather uneventful recovery following the first craniotomy, was able to return to school and did fairly well in her school work. She had that one incident prior to her most recent admission to the hospital, during which time her home-town physician treated her appropriately and to which she responded rather favorably. Several months later, on reexamination, because of recurrent severe headaches, lassitude, and vomiting, she was readmitted. The comparison of the lateral films, taken initially in 1957, and the more recent ones taken in November, 1960, show further increase in the size of the sella, which again is symmetrically enlarged, and again with either the same intra-sellar calcification or another. I'm inclined to believe that this was the same calcification which had not been resected at the time of the first craniotomy.

At the time of the first exploration, the optic chiasm was prefixed. There wasn't a tremendous bulge from the sella by the cystic mass. It was apparent, and the right optic nerve on the right side of the chiasm was elevated more than the left. The approach between the anterior clinoids and the anterior aspect of the chiasm, was done rather carefully, hoping that visual acuity would not further be reduced. However, the child did go on for 3½ years fairly well until November, 1960. Then on readmission, the second admission, the temporal hemianopsia prevailed and persisted in the left eye with total blindness in the right eye, no light perception.

This film shows a section through the cyst wall duct. Dr. Bucalo, would you want to discuss it?

DR. BUCALO: Well, it simply is a part of the cyst wall and shows the epidermal lining and the little aspect on the right, where the arrow is now, had a very thin layer of basal cells which showed no proliferation at all. The epithelial lining, the connective tissue wall, was a little bit edematous and infiltrated by a few mononuclear cells, a rather characteristic picture of the basic structure found in this region.

DR. DANIELS: This film shows an area of calcification in other parts of the lesion. There is some loss of integrity of the wall of the cyst. You can see here it is disorganized and a cellular infiltrate is a little more increased.

And this shows the cholesterol in the sections. The cholesterol has been washed out in the thickening procedure, and all that is left is the clefts formed by the crystals which once resided in those spaces you can't see. At the rim of almost every one of those cleft spaces are clefts of the nuclei which represent the foreign body type, multinucleated giant cells which appear as a result of the presence of these cholesterol crystals which provoke this type of cellular reaction. The child is now 13 years of age. This photograph was taken just a week ago. I think you can see the evidence of adiposity.

On closer inspection, we see that both pupils are widely dilated. The right globe is somewhat deviated to the right. She is totally blind in the right eye and is able to see with only the nasal half of the left visual field. She gets around very well. She has returned to school. She isn't bothered by her visual deficit oddly enough, although this is characteristic of children who bear the visual impairment fortunately quite well.

This film shows the incision of the craniotomy which extends in horseshoe-shaped fashion. Thank you.

DR. FRIED: Any questions?

DR. BAER: I wasn't quite sure whether only part of a tumor was removed at the first operation, and then progressed.

DR. DANIELS: Well, the first operation did not take all the solid portion of the tumor. In the second one, all the solid portion that could be encountered was delivered. The chiasm was displaced backward. The bulging cyst wall taken down to a finer level was much more accessible and a relatively large portion of the tumor was removed.

QUESTION: Dr. Daniels, what is the prognosis?

DR. DANIELS: This is a benign congenital neoplasm, as you know. It's extremely tragic for this child that she lost vision totally in the right eye. If this tumor could be delivered completely within the cyst wall, the child could be cured. I don't believe that I removed the tumor entirely. It is extremely difficult. When you do, there's one monograph which shows a total removal but this was followed promptly by death. Ultimately, unfortunately, this child will succumb to this tumor.

QUESTION: I think with all the signs, difficulty with vision, headache, vomiting and signs of increased intracranial pressure, logically one should have suspected craniopharyngioma with evidence of visual disturbances, and I am wondering how often this occurs?

DR. DANIELS: I don't have a large series but these signs are quite true and I think this case is characteristic of those Dr. Cushing reported in his series of cytologically verified neoplasms, many of which were operated on by the sub-cortical route, and did die. The great majority of these children have some form of marked visual difficulty but the thing that brings them to the hospital is severe headache and vomiting.

DR. FRIED: Dr. Greenspan?

DR. GREENSPAN: Dr. Daniels, how much of the pituitary was sacrificed, how much of the hypothalmus was sacrified? Is this child receiving any supportive therapy that would help to maintain her? I noted she had a "hyponatremia" recently and was given hydrocortisone which may or may not necessarily keep that sodium level up. Does she need any therapy to keep her from having manifestations?

DR. DANIELS: Answering your question regarding the hypopituitarism, this wasn't disturbed at all. One didn't actually see the pituitary but the cyst itself lies external to the pituitary, and the pituitary is compressed. It's not invaded. The tumor arises usually from the infundibulum, and the function of the pituitary is depressed by reason of this compression. The child has a mild, moderate diabetes insipidus for which initially, post-operatively, she was treated with Pitressin. Presently, she's existing on practically nothing by way of replacement, drinks a coca-cola between breakfast and lunch, and perhaps another pop or glass of water between lunch and dinner. She gets up to void approximately once or twice a night and that's the essential difficulty at present.

QUESTION: I notice that the calcification shown originally in the first film is still present in the second. Is that calcification in the pituitary?

DR. DANIELS: No, it's calcification in the tumor, directly in the sella. If this tumor expands, it does so at the expense of the space occupied normally by the hypophysis and the contents, the size of the sella is increased.

DR. FRIED: Any further questions or comments? Thank you, Dr. Daniels.

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